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COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
SINGH, ANOOP KUMAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,308	GROSVELD, FRANK	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,7,8,10,11,33-36,39 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4,7-8, 10-11, 33-36, 39-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/25/07, 2/5/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed February 5, 2008 has been received and entered. Applicants have amended claims 2, 4, 7-8, 10, 33-36, while claim 1, 3, 5-6, 12-32, 37-38 have been canceled. Applicants have also added claims 39-40 generally directed to elected invention.

Claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 are pending in this application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/5/2008 has been entered.

Election/Restrictions

Applicant's election with traverse of group I in the response filed dated April 27, 2006 was acknowledged. The traversal was on the grounds that Group I and Group II-III should be examined together because search for invention of Group I would be coextensive with Group II and III. In addition, applicants asserted that only method of Group I would be required to make the antibody recited in Groups II and III. Applicant's arguments for examining elected method group with the product claims were not persuasive for the reasons of record (see office action dated 2/12/2007).

Claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 are under consideration.

Maintained-Drawings

The replacement drawing submitted on 2/5/2008 is not accepted by the Examiner and is objected to as failing to comply with 37 CFR 1.84(p)(5) because replacement drawing fails to indicate loxP site described in the original filed drawing: "Replacement Sheet". Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. In the instant case, applicants have cited multiple references in the specification but they have not been considered by the Examiner as no copy of any of the publication was provided.

Priority

It is noted that instant application is a continuation (CON) of PCT/IB02/02303 filed on 04/24/2002 which claims benefit from application

GB0110029.6 filed in Great Britain on 4/24/2001. Upon review of the disclosure of the prior-filed provisional application filed in GB fails to provide descriptive support for lox P site disclosed in the instant specification and embraced by the breadth of instant claims 2, 4, 7-8, 10-11, 33-36, 39 and 40. Claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 are not enabled in all the applications from which applicant is claiming benefit of priority. There is not adequate support or enablement for claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 in the manner provided by the first paragraph of 35 U.S.C. 112 in prior filed provisional applications to a method for producing single heavy chain antibody. In case, if applicants have evidence to support otherwise, applicants are invited to indicate page and line number for the written support as recited in claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 of the instant application. Therefore, the effective filing date for instant claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 is 04/24/2002.

Oath/Declaration

The Weiner declaration on February 5, 2007 under 37 CFR 1.132 filed is sufficient to overcome the rejection of claims 1-2 based upon reference of Ledbetter et al (WO 99/42077, dated 08/26/1999, IDS) applied under 102(b).

The declaration filed on February 5, 2007 under 37 CFR 1.132 is not sufficient in part to overcome the rejection of claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 upon declaration of Dr. Weiner, applied under 35 U.S.C. 112 First paragraph. The declaration will be discussed in detail below as it applies to the rejection.

The Grosveld declaration on February 5, 2007 under 37 CFR 1.132 filed is not sufficient in part to overcome the rejection of claims 2, 4, 7-8, 10-11, 33-36, 39 and 40, applied under 35 U.S.C. 112 First paragraph. The declaration will be discussed in detail below as it applies to the rejection.

The Drosschedi declaration on February 5, 2007 under 37 CFR 1.132 filed is not sufficient to overcome the rejection of claims 2, 4, 7-8, 10-11, 33-36, 39 and 40, applied under 35 U.S.C. 112 First paragraph. The declaration will be discussed in detail below as it applies to the rejection

Terminal Disclaimer

The terminal disclaimer filed on June 25, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US non provisional application no 10/692,918 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Objections

Claims 7-9 and 11 are objected to because of the following informalities: In the instant case, dependent claims recite "a method according to claim.." which should be changed to "The method of claim 2... Appropriate correction is required.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods for producing single heavy chain antibody in a nonhuman mammal by expressing a heterologous VHH locus comprising VHH exon, D, J exon , a constant heavy chain comprising at least one constant heavy chain gene, wherein each of said at least one constant heavy gene when expressed does not express a functional CH1 domain.

In analyzing whether the written description requirement is met for the genus claim, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. The claims embrace producing single heavy chain antibody in a nonhuman mammal of any species expressing a VHH locus comprising a constant heavy chain gene when expressed does not express a functional CH1 domain.

The specification describes that a VHH or camelised VH single chain antibody does not possess a functional CH1 domain nor a functional CH4 domain (see page 8, lines 22, page 9, line 6-7). The specification also describes that the single heavy chain antibody loci have one or more genes which do not express functional CH1 or CH4 domains that may occur by mutation, deletion substituted or other treatment of the CH1 and CH4 exons of the constant heavy region gene (see page 11, lines 27-30). The specification teaches that the transgenic mammal according to the present invention is smaller than a Camelid, preferably it is selected from the groups consisting of: a mouse, rat, guinea-pig, hamster, monkey and rabbit. Additionally, the specification discloses that a camelised VH exon/region may be a naturally occurring VH coding sequence derived from mammals other than Camelids or any homologue, derivative or fragment of the exon as long as the exon/region can recombine with a D region/exon, a J region/exon and a constant heavy chain region (see page 9, line 24-page 10). Similarly D exon and a J exon may

also include naturally occurring sequences of D and J exons from Camelids or other species of mammals (see page 10, lines 19-27) and constant heavy chain region may also be from either rabbit, mouse or human (see page 12). Thus, instant claims embrace plurality of different combination of hybrid transgenic loci to generate plurality of different hybrid single heavy chain antibody. The specification is silent, however, on any homologue, derivative or fragment of an exon or a region that could recombine with a D, J region/exon or on any specific mutation, substitution or deletion resulting non functional CH1 and or CH4 that would produce the contemplated single heavy chain antibody in any nonhuman chimeric or transgenic animal. The specification additionally fails to disclose the nature of the association of presence and or absence of other possible elements such as Cμ, Cδ, Cα, Cε, Cγ in the VHH or camelised VH loci. The claims thus constitute a genus that encompasses plurality of hybrid loci comprising mutation, substitution or deletion of constant heavy chain gene that would produce single heavy chain antibody in plurality of different chimeric or transgenic nonhuman mammal yet to be discovered, and since the specification does not discloses any single species of the VHH loci that may be capable of producing a single heavy chain antibody in any species of nonhuman mammal, the disclosed general structural features do not constitute a substantial portion of the claimed genus encompassing combination of hybrid loci with plurality of mutation, substitution or deletion of CH1 and other elements as described above. As such, the Artisan of skill could not conclude that Applicant possessed any species. Hence, none of the claimed species could be demonstrated as possessed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure of the VHH loci such that the Artisan of skill could determine the desired effect could be achieved in the nonhuman mammal. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus of transgenic loci for contemplated biological activity in plurality of different nonhuman mammal.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The breadth of the claims reads on producing single heavy chain antibody in any nonhuman mammal that express heterologous VHH loci or camelised VH loci that comprises at least one constant heavy chain when expressed does not express a functional CH1 domain that may occur by mutation, deletion substituted or other treatment of the CH1 and CH4 exons of the constant heavy region gene (see page 11 of the specification). However, specification fails to provide any specific guidance on structure of any of the resulting transgenic hybrid loci that would produce single heavy chain antibody. Recently, Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art o record) disclose introducing Ig loci comprising two llama VHH region, all the human D and JH region, human Cμ, Cδ, Cγ2 and LCR in μMT transgenic mice that showed the

presence of CH1 exon which was spliced out without any chimeric Ig expression (figure 7). Janessens et al emphasize that splice mutation at the 3' CH1 border is insufficient for CH1 removal and therefore more than this point mutation is required. The specification fails to correlate specific elements of the VHH loci that should be deleted substituted or mutated resulting in formation of functional single heavy chain antibody in response to challenge to antigen. The claimed invention as a whole is not adequately described since claims read on plurality of different combination of hybrid loci comprising mutation, substitution or deletion of constant heavy chain gene and other elements and specification fails to describe any species that would produce any functional single heavy chain antibody in any nonhuman mammal and which is not conventional in the art as of applicants effective filing date. In view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the transgenic hybrid loci having different elements derived from different species of nonhuman mammal with plurality of different mutation, substitution or deletion of heavy chain gene. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

The skilled artisan cannot envision the detailed chemical structure of the encompassed VHH loci that comprises specific elements that are deleted, mutated or substituted in any nonhuman mammal, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of

the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of producing single heavy chain antibody into any nonhuman mammal at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

New Grounds of Claim Rejections -35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 7-8, 10-11, 33-36, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of

the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Nature of the Invention:

The claims are directed to a method for the production of a single chain antibody in a non human mammal comprising expressing a heterologous VHH heavy chain or a camelised VH heavy chain locus in that mammal specifically in B cells in response to antigen challenge. In further embodiments, VHH single heavy chain locus comprises a camelid VHH, at least one D exon of human origin and at least one J exon and constant region of human origin. Claims 39 and 40 limit the method of claim 2 and 4 to rodent and the regulatory sequence is locus control region respectively.

Breadth of the claims:

The claims are broadly directed to produce single chain antibody in any non human mammal by expressing a heterologous VHH or a camelised VH heavy chain locus in the mammal in B cell in response to antigen challenge. The breadth of the invention embraces expressing chimeric loci comprising one or more genes that do not express functional CH1 or CH4 domains. This may occur by mutation, deletion substituted or other treatment of the CH1 and CH4 exons of the constant heavy region gene in any nonhuman mammal. Thus, breadth of instant claims embraces

chimeric loci with multiple permutation and combination of mutation, deletion substitution of CH1 and CH4 exon. Additionally, given broadest reasonable interpretation, instant methods read on expressing the VHH or a camelised VH locus comprising a regulatory sequence providing expression specifically in B cell by somatic gene delivery, using embryonic stem cell, nuclear transfer or pronuclear injection. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of these, aspect must be shown to a reasonable extent so that one of the ordinary skills in the art would be able to practice the invention without any undue burden being on such Artisan.

Guidance of the Specification and The Existence of Working Examples:

The specification contemplates using vector such as YAC or BAC that is suitable of inserting large amounts of nucleic acid, sufficient to encode an entire immunoglobulin heavy chain locus (page 15, lines 14-23). The specification contemplates eukaryotic promoters such as alpha-actin, beta-actin, tubulin promoters or, a tissue-specific manner such as promoters of immunoglobulin genes. In addition, specification also discloses Moloney murine leukaemia virus long terminal repeat (MMLV LTR) promoter, the Rous sarcoma virus (RSV) LTR promoter or the human cytomegalovirus (CMV) IE promoter promoters that may also be used (see para. 101 of the published specification). The specification further contemplates using any of these promoters that are modified by the addition of further regulatory sequences such as tissue-specific enhancers capable of regulating expression in antibody-producing cells (see para. 102). The specification asserts loci and vectors may be introduced into an animal to produce a transgenic animal. It is noted that method of inserting the loci into the genome of a recipient animal will be achieved by microinjection or by introducing DNA into embryonic stem cells (ES) cells which can be inserted into a host embryo to derive transgenic mice (page 27, lines 21-31 bridging to pp 28 see entire section). The specification further

contemplates nuclear transfer technique for introducing DNA into any cell. The nuclei of these cells are used to replace the nucleus of a fertilized egg which may be of any species to give rise to transgenic animals (see page 28, lines 3-6). It is noted that specification defines a VHH or camelised VH single chain antibody that does not possess a functional CH1 domain nor a functional CH4 domain (see page 8, lines 22, page 9, line 6-7). The specification also contemplate that the single heavy chain antibody loci have one or more genes which do not express functional CH1 or CH4 domains that may occur by mutation, deletion substituted or other treatment of the CH1 and CH4 exons of the constant heavy region gene (see page 11, lines 27-30). It is additionally noted that while describing general techniques, the specification describes at least two loxP sites in a locus for the deletion of IgM and IgD heavy chain genes if required (see page 21, line 21-23) suggesting that deletion of IgM or IgD in vector construct was just a hypothesis (also see provisional application filed in Great Britain, page 11, lines 22-25) that was not reduced to practice at the time of filing of this application, as neither art nor as filed specification specifically teach the specific elements in the transgenic loci that are either substituted, deleted or mutated in the method of producing single chain antibody in any non human mammal.

Applicant's example provides only a schematic of the construct and various techniques without disclosing any specifics mutation, deletion or substitution in the construct (see page 24) that would have resulted in production of single heavy chain antibody in amount sufficient to be isolate from any non human mammal.

State of the Art and Predictability of the Art:

The state of the art at the time of filing of this application recognizes that only IgG2 and IgG3 single heavy chain antibodies are produced in camelids (see Hamers-Casterman et al, Nature, 363:446-448, 1993.). The art teaches that camelid γ2 and γ3 chain are considerably shorter than normal mammalian γ or camel γ1 chains which was found to be absence of CH1 domain (see figure 3 and page 448,

col., 1 para. 2). The state of art at the time of filing of this application was generally silent with respect to development of B-cells expressing VHH camelid antibodies (De Genst et al, Dev Comp Immunol. 2006; 30(1-2): 187-98, art of record). It was not known whether the IgM pathway is bypassed, or else it occurs by some other specialized cell population or any specific factors are requires for the assembly and expression of VHH single chain antibodies. As stated in previous office action earlier work in the filed showed functional human VH domains that could be selected from randomized phage display libraries and that rearranged heavy chain genes engineered to be devoid of CH1 domain can be expressed (see Riechmann et al J Immunol Methods. 1999; 231(1-2): 25-38, art of record and Sitia et al Cell. 1990 Mar 9;60(5):781-90, art of record). These observations suggest that at the time of filing of this application, prior art was generally silent with respect to generating single heavy chain antibody in a non human mammal. Prior to instant invention it was generally known that humanized antibodies undergo lymphoid-specific gene rearrangement and only a small proportion of mouse B cells expressed the human immunoglobulin chains. The miniloci contributed poorly to serum immunoglobulin which is attributed to competition between the transgenic and endogenous immunoglobulin loci (See Wagner et al abstract Nucleic Acids Res. 1994; 22(8):1389-93 and reference therein). Furthermore, art also teaches low level of B cell expressing immunoglobulin chain is attributed to competition between the introduced minolocus and the endogenous immunoglobulin mouse locus (see Wagner page 1389, col. 2, para. 2). In the instant case, neither specification nor the declaration provided any guidance that an appropriate serum titer could be achieved in response to antigen challenge in a wild type chimeric nonhuman mammal. In fact, one of skilled in the art would have to perform undue experimentation to characterize single heavy chain antibody if produced in wild type nonhuman mammal in response to antigen challenge in order to make use of the invention. In the instant case, as written, claims embrace any method to

express a heterologous VHH heavy chain locus comprising a constant heavy chain region comprising at least one constant chain gene, wherein each of said at least one constant heavy chain gene when expressed does not express a functional CH1 in a non human mammal. It is noted that specification contemplated that the single heavy chain antibody loci have one or more genes that does not express functional CH1 or CH4 domains, which may occur by mutation, deletion substituted or other treatment of the CH1 and CH4 exons of the constant heavy region gene (see page 11, lines 27-30). However, the specification does not provide any guidance with respect to construct comprising various elements that would results in production of single heavy chain antibody in any nonhuman mammal. Similarly, the specification does not provide any guidance on which combination of CH1 and/ CH4 domain must be deleted, substituted or mutated in order to produce functional single heavy chain antibody in any non-human mammal. The specification admits that "presence of the lox sites allows the deletion of IgM and IgD heavy chain genes if required" (supra). In fact several years after filing of instant application, Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art of record) disclose Ig loci with two llama VHH region, all the human D and JH region, human Cμ, Cδ, Cγ2 and LCR introduced in μMT transgenic mice still show the presence of CH1 exon which was spliced out and no chimeric Ig expression (figure 7). Janessens et al emphasize that lack of CH1 is crucial for HCAb secretion, but the camelid splice mutation at the 3' CH1 border is insufficient for CH1 removal, thus more than this point mutation is required (see page 15134, col. 1, para.2). This indicates that at the time of filing little was known in the art about the specific deletion, mutation and or substitution that would show contemplated biological activity. It is emphasized knowing that rearranged heavy chain genes engineered to be devoid of CH1 domain does not necessarily tell you all the different combination of deletion, mutation or substitution that would result in functional single heavy chain antibody and because more than point mutation is required. It is noted that the unpredictability

of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991)*. It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991)*. The lack of guidance in the specification would force the skilled practitioner to guess and try different combinations in the construct to make transgenic nonhuman mammal and then characterize any resulting single heavy chain antibody to practice the invention. Such guessing would require extensive and undue experimentation. Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

The specification asserts loci and vectors may be introduced into an animal to produce a transgenic animal. It is noted that method of inserting the loci into the genome of a recipient animal will be achieved by microinjection or by introducing DNA into embryonic stem cells (ES) cells which can be inserted into a host embryo to derive transgenic mice (page 27, lines 21-31 bridging to pp 28 see entire section). However, as stated in previous office action, the state of the art is such that ES cell technology is generally limited to the mouse system and that only putative ES cells exist for other species (Moreadith et al., J. Mol. Med., 1997 p214, abstract, Hochepied et al (Stem Cells, 2004, 22, 441-447; abstract, both art of record). Thus, in view of the prior art and lack of guidance provided in the specification, only mouse ES cells were available at the time of filing of this application. It is also noted that specification further contemplates nuclear transfer technique for introducing DNA into any cell. The nuclei of these cells are used to replace the nucleus of a fertilized egg which may be of any species to give rise to transgenic animals (see page 28, lines 3-6). However, state of art summarized by the references

of Wolf et al (Journal of Biotechnology 65: 99-110, 1998); Stice et al (Therigeneology, 1998, 49: 129-138); disclose limitation of routine method of nuclear transfer. For instance, Wolf et al emphasize several factors that influence embryo cloning by NT, such as the state of development and cell cycle of the donor cells, the choice of recipient cell, the method of activation of oocyte (see entire article). The specification does not provide any guidance to these parameters. Stice et al reported timing of embryonic genome activation might be partly responsible for species-specific differences. Stice et al further noted that method used for cloning sheep where the donor cell was in G0 could not be used in other animal species (see the last paragraph on page 131). This clearly suggests that method used in one animal or species could not be used in another animal or species, the specification does not provide any guidance how claimed method would be practiced. The specification does not provide any guidance with respect to overcome this art recognized unpredictability with respect to express any loci in any nonhuman mammal using any one of these method. An artisan would have to perform undue experimentation to make and use the invention commensurate with full scope of the invention without reasonable expectation of success.

Given the broadest reasonable interpretation, claimed method also read on producing single heavy chain antibody in any nonhuman mammal by somatic gene delivery. While progress has been made in recent years for in vivo gene transfer, however, vector targeting in vivo to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that could not have been overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's

compartmentalization within the cell, or its secretory fate, once produced (Ecke et al Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101, also see Nature Biotechnology, 2006, 24, 3, 305-306). Additionally, in the instant case, issue is not a matter of simply delivering the transgenic loci into a tissue. The issue involves how many B cells in the target body is being transduced and most importantly whether an effective level of gene is expressed for sustained period of time such that immunization results in production and subsequent isolation of single heavy chain antibody against an antigen that could be isolated. The specification and prior art is generally silent with respect to generating antibody by administering the heterologous loci in any nonhuman mammal by somatic gene delivery. An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success. Claims 2, 4, 7-8, 10-11, 33-36, 39 are directed to a method for producing a single chain antibody in a nonhuman mammal by expressing a heterologous VHH single chain locus specifically in B cells in response to antigen challenge. As stated before claim read on somatic gene delivery. The specification contemplates using promoters that are modified by the addition of further regulatory sequences such as tissue-specific enhancers capable of regulating expression in antibody-producing cells (see para. 102). The art teaches variable effects of different promoters depending upon site of expression. Maruyama et al (US Patent application 20050070014, art of record) disclose that the choice of the promoter is instrumental for transgene expression and that the promoter (see para. 93 of the published application). At the time of invention, art of record recognized only the mouse as a routinely manipulated animal and recognized the unpredictability of making transgenic animals other than mice using any promoter or construct. For example, Keefer (Animal Reproduction Science 82-83: 5-12, 2004) recognizes the inefficiency of pronuclear microinjection transgenic techniques and the unpredictability of transgene expression when applied to generating transgenic cows, goats and sheep,

for example (see page 6, para. 1, line 1 to page 7, line 4). In fact, guidance provided in the applicant's cited post filing art of Janssens et al also describe the difference in results from those obtained by Zou et al with respect to the role of LC rearrangement *(*J Immunol, 2005*, 175:3769–3779)* to level of expression of the locus (and, thus, signaling). Janssens et al attributes this difference in results to use of LCR in the constructs (see page 15134, col.2, para.1). Given that a given construct may react very differently from one species to another, one of skill in the art would have been required to undergo undue experimentation to determine which promoters and specific elements of transgene constructs would produce the desired expression of VHH single heavy chain locus in all different nonhuman mammals as broadly recited delivered via any route. It is emphasized that art teaches unpredictability associated with gene delivery and variable expression pattern. There is no evidence on record that transgenic loci delivered via intramuscular or intravenous route or other any other route would result in adequate expression of the VHH loci in B cells. The specification does not provide nexus between expression levels to any enabled use of low level production of antibody in response to antigen as embraced by the breadth of the claimed method. In the instant case, the specific elements contemplated by the specification in the construction of vector for use are specifically directed to generating the transgenic mouse which were not discovered by Applicant, rather they were derived from the prior art based on reports of their function in mice. Absent of evidence to the contrary, it is not clear that these elements (LCR or B cell specific promoters) would be functional in other animal species using any other method of construct delivery in the same manner as they have been demonstrated in the transgenic mouse produced by pronuclear injection of the construct. Thus, the art of record at the time of the invention does not provide enabling support for the claimed invention of making and using nonhuman mammal commensurate with full scope of the claims. An artisan would have to perform undue experimentation to empirically test different elements of the

construct to specifically express the VHH heavy chain in B cells of different species by delivering the loci using other method that are embraced by the breadth of instant claims to make and use the invention.

The Amount of Experimentation Necessary:

The claims are directed to broadly producing single heavy chain antibody in any nonhuman mammal by expressing a heterologous VHH heavy chain locus in B cells in response to an antigen challenge, wherein VHH heavy chain locus comprises VHH exon, D and J exons, constant chain gene comprising at last one constant heavy chain when expressed, does not express a functional CH1 domain; however, the specification is not enabling for this breadth. For instance, given broadest reasonable interpretation claim read on expressing heterologous VHH heavy chain in non human mammal by any method, while the art clearly shows that expression of VHH heavy chain locus would be unpredictable by many of the contemplated methods such as somatic gene delivery, use of ES cell or nuclear transfer as embraced by the breadth of the claim. Additionally, claims embrace a VHH locus that comprises at least one constant heavy chain gene comprising at least one constant heavy chain gene when expressed does not express a functional CH1 domain. In a preferred embodiment, specification describes nucleic acid encoding the CH1 and CH4 domain is mutated, deleted or substituted or otherwise treated so that the constant heavy chain of expressed VHH single chain antibodies does not contain a functional CH1 domain and a CH4 domain (supra and see specification page 11). The working examples are preliminary and claimed VHH loci comprises all possible combination of deletion, substitution and mutation of CH1 and/or CH4 with presence and or absence of other possible elements such as Cμ, Cδ, Cα, Cε, Cγ. An artisan would have to perform undue experimentation to test different VHH loci in expressing single heavy chain loci in any nonhuman mammal particularly since Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art o record) disclose Ig loci with two llama VHH region, all the human D and JH region,

human Cμ, Cδ, Cγ2 and LCR introduced in μMT transgenic mice still show the presence of CH1 exon which was spliced out and no chimeric Ig expression (figure 7). Janessens et al concurred with previously know fact that lack of CH1 is crucial for HCAb secretion, but demonstrated that splice mutation at the 3' CH1 border is insufficient for CH1 removal and therefore more than this point mutation is required (see supra). The specification fails to correlate specific elements of the VHH loci that may result in formation of single heavy chain antibody in response to challenge to antigen. The specification does not provide sufficient guidance to overcome this unpredictability for practicing the claimed method in any nonhuman mammal. Thus, skilled artisan would have to empirically test the method by making VHH loci with plurality of different elements and then test each one of them that reliably express in a non human mammal by delivering the construct by plurality of different methods set forth in specification and then characterize any resulting single heavy chain antibody that may be complexed with animals' endogenous antibody to make use of any such antibody without reasonable expectation of success as supported by the observations in the art record.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions.

Response to Arguments

Applicant's arguments and declaration filed on February 5, 2008, have been fully considered but they are not fully persuasive.

With respect to applicants' observation that the copy of the Interview summary received by the applicants did not include a copy of the draft amendment (see page 7), it is noted that Examiner had submitted the summary of Interview as well as copy of draft amendment for mailing which is evident from the availability

of both the document on the Image File Wrapper. The processing of document in mailroom inadvertently may have omitted the document from mail, however, if applicants wish to receive the same it could be again mailed to the applicant.

Applicants' arguments and declaration by Drs. Louis M. Weiner and Grosveld providing evidence that the expression of the other locus (MΔGΔ) in a wild type mouse background (Grosveld Declaration, paragraph 5, Figure 1-2, Weiner declaration pages 4 and 5) is persuasive in part. Examiner would agree to the extent that disclosed transgenic loci could be expressed in wild type mouse to produce single heavy chain antibody to the extent one of skilled in the art would have to empirically test whether resulting single heavy chain antibody is complexed with endogenous antibody of wild type nonhuman mammal and an adequate titer of the antibody is produced in response to antigen challenge in order to make use of the invention. Prior to instant invention it was generally known to one of ordinary skill in the art that humanized antibodies undergo lymphoid-specific gene rearrangement and only a small proportion of mouse B cells expressed the human immunoglobulin chains. The miniloci thus contributed poorly to serum immunoglobulin which is attributed to competition between the transgenic and endogenous immunoglobulin loci (See Wagner et al for a general review Nucleic Acids Res. 1994; 22(8):1389-93). In the instant case, the issue is not whether transgenic loci could be expressed in B cells of wild type animal rather issue is whether adequate titer of single heavy chain antibody could be produced in any nonhuman mammal in response to antigen challenge to make use of the invention. The expression of single heavy chain antibody on reduced western blot gel does not provide enabling support to one of skilled in the art that adequate titer of contemplated single heavy chain antibody could be produced in any wild type nonhuman chimeric mammal to make use of any such antibody. The specification does not provide any guidance to characterize any resulting single heavy chain antibody. Additionally, as stated before, applicants are relying for a post-filing art

in support of enablement showing Applicants have generated both single heavy chain antibodies in mice using specific transgenic loci MΔGΔ, GΔ and MGΔ as disclosed by Janssens et al (PNAS, 103, 15130-15135, art of record). As an initial matter, applicants' argument and declaration by Drs. Louis M. Weiner and Grosveld are not commensurate with full scope of the claim. In the instant case, contrary to applicant's arguments claims are not limited to any specific loci expressed in any transgenic or wild type mouse rather it embraces producing single heavy chain antibody in any nonhuman mammal that express heterologous VHH loci or camelised VH loci that comprises at least one constant heavy chain when expressed does not express a functional CH1 domain that may occur by mutation, deletion substituted or other treatment of the CH1 and CH4 exons of the constant heavy region gene (see page 11 of the specification). However, specification fails to provide structure of transgenic loci disclosed by Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art of record) who in post filing art emphasized that splice mutation at the 3' CH1 border is insufficient for CH1 removal and therefore more than point mutation is required. Janessens et al disclose Ig loci with two llama VHH regions, all the human D and JH region, human Cμ, Cδ, Cγ2 and LCR introduced in μMT transgenic mice showed the presence of CH1 exon which was spliced out and without any chimeric Ig expression (figure 7). It is the specification, not the knowledge of one skilled in the art, which must supply the novel aspects of an invention in order to constitute adequate enablement." (See *Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)*). It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966).* Contrary to applicant's assertion instant disclosure provides general strategies that embrace plurality of different mutation, deletion substitution or other treatment of the CH1 and CH4 exons of the constant heavy region gene with

or without other element Cμ, Cδ, Cγ2, Cε and Cα. Applicants are required to indicate the support for transgenic loci in the specification that includes Cγ2 and Cγ3 with CH1 deleted, one with CH1 deleted with Cμ and another without Cμ and Cδ when introduced via any route in a nonhuman mammal resulting in formation of adequate titer of single heavy chin antibody in response to antigen challenge to make use of the invention . Examiner has provided adequate prior art to show several non enabling embodiments that are embraced by the breadth of the claims.

Applicant asserts and provides declaration by Dr. Weiner against De Genst et al reference showing that it has been countered by Janssens et al. In response, it is noted that De Genst references is included to show the state of the art several years after filing of this application. Examiner would agree that Janssens et al shows functional expression of several mu and gamma single heavy chain isotypes, all of which bind antigen (Weiner Declaration), however, declaration by Dr. Weiner is not commensurate with the scope of the claims as instant claims are not limited to the scope of transgenic mouse taught by Janssens, instead they encompass plurality of different mutation, substitution or deletion of CH1 and CH4 exon that may or may not result in formation of single heavy chain antibody.

Applicants provide portion of the paragraph regarding Janssens et al. submitted with the previous response addressing preparation of the animals, including citations to Applicant's application as filed. With respect to expression of loci containing IgM and IgG, and IgG only (page 7, line 21, through page 8, line 3, see arguments page 15); it is noted that specification describes VHH heavy chain locus comprises at least one VHH region each comprising one VHH exon, at least one D region each comprising one D exon and at least one J region each comprising one J exon, wherein the VHH region, the D region and the J region are capable of recombining to form VDJ coding sequence, (b) a (any) constant heavy chain region comprising at least one Cγ constant heavy chain gene, and which when expressed does not express a functional CH1 domain nor a functional CH4 domain, (c) at least

one recombination sequence (rss) capable of recombining a J region of step (a) directly with a (any) Cγ constant heavy chain gene of step (b). The specification at the indicated pages describes the mechanism of involves recombining the J region of step (a) directly with any Cγ heavy chain region gene of the constant heavy chain region of step (b). The disclosure does not limit the recombination of J region to any specific Cγ1-4 heavy chain region. Additionally, it is also not clear from this locus how CH1 and CH4 are made nonfunctional. The specification does not provide guidance at the indicated page a VHH locus comprising Cγ2 and Cγ3 with only CH1 is deleted and one CH1 deleted Cμ as described by Janssens (see figure 1 bottom). Additionally, applicants' argument for support of any specific loci disclosed by Janssens is not commensurate with the scope of the claims. In the instant case, claims are broad and require a constant heavy chain region comprising at least one constant heavy chain gene wherein at least one constant heavy chain gene when expressed does not express a functional CH1. This could be achieved by mutation at CH1 boundary, substitution or deletion of any one of the constant heavy chain gene. Post filing art of Janssens reported that camelid splice mutation at the 3' CH1 border is insufficient for CH1 removal, thus more than mutation is required. An artisan would have to perform undue experimentation to try different combination of substitution, mutation or deletion of CH1 and or CH4 domain to produce single chain antibody without reasonable expectation of success.

With respect to human constant region (Figure 1 and page 11, lines 1-11), lacking CH1 (page 11, lines 9-11 and page 24, lines 17-20), with two camelid VHH regions and human D and J regions (page 12, lines 13-19) in mice (page 28, line 3). Bac clone 11771 and pFastBac were both used successfully (page 22, lines 4-5). The loci further contained FRT and LoxP sites (page 21, lines 16-19), and immunoglobulin LCR (page 23, lines 12-14) (see page 15 of the argument), it is noted that applicants are using different embodiments from different part of the specification to establish the transgenic locus comprising specific elements to

produce single heavy chain antibody in a nonhuman mammal in response to an antigen challenge. As an initial matter applicants' argument and support is not commensurate with the scope of the claim as described in previous section. Furthermore the elements upon which applicant relies (i.e., Cγ2, Cγ3, further contained FRT and LoxP sites, LCR) are not recited in the any one of the independent claims. Additionally, specification at the indicated page describes construction of vector (page 24, see steps a-e, also see figure 1-3 in application GB0110029.6) that includes following steps (a) endogenous mouse locus if inactivated (b) The DJ and IgM region (c) VHH (d) LCR and (e) Ch1 and /or CH4 domain encoded by their respective exon is rendered non functional by homologous recombination or by removing splice acceptor sequence. Upon review of provisional application filed in GB, it appears that instant disclosure for construction of vector (Figure 1 of instant application, Figure 1-3 of provisional application) does not exclude IgM or IgD. In fact vector method by this process does not require any loxP sites which is also evident from the disclosure in the provisional application (see Figure 2 and 3). The vectors disclosed on page 24 of the instant specification injected into fertilized mouse eggs of animals (page 27, lines 24-30) that do not produce surface IgM and have a block in B cell development at the pre-B cell stage *(see* page 28, lines 23-28 and Figure 1), and in wild type mice (page 27, lines 21-23) is different then one disclosed by Janssens that require all containing Cγ2 and Cγ3 with CH1 deleted, one with Cμ and Cγ (MGΔ), one without Cμ and Cδ (GΔ), and one with CH1 deleted Cμ (MΔ GΔ). An artisan would have to first make different transgenic loci and then test each one by making transgenic animal and then characterize any single heavy chain antibody produced therefrom. With respect to applicants' argument that one could achieve position independent expression through the use of, for example, LCRs, it is noted that independent claims do not require LCR. Therefore rejection to claims 2, 4, 7-8, 10-11, 33-36, 39 is maintained for the reasons of record.

Applicant also argues that without LCRs, the technology the method will still work, expression is less efficient and more variable, and more animals may need to be screened.

In response, it is emphasized that it is not the question whether method without LCR would still work; the issue is art teaches inefficiency of pronuclear microinjection and the unpredictability of transgene expression when applied to generating transgenic cows, goats and sheep, for example (see page 6, para. 1, line 1 to page 7, line 4) with respect to use of these animal as bioreactor. In fact applicant's cited post filing art of Janssens et al also describe the difference in results from those obtained by Zou et al with respect to the role of LC rearrangement *(*J Immunol, 2005*, 175:3769–3779)* to level of expression of the locus (and, thus, signaling). Janssens et al attributes this difference in results to use of LCR in the constructs (see page 15134, col.2, para.1). In absence of any requirement of LCR in independent claims specific guidance and given species-specific differences in the expression of various transgenes, an artisan would have to perform undue experimentation and make new inventions in order to make use of the invention. Examiner would agree with applicants' assertion and declaration by Dr. Drosschedi that use of LCR and human heavy and light immunoglobulin gene loci that have also been expressed as transgenes in cattle (Kuroiwa et al, Nat Biotech., 2002; 20:889-894, art of record) was known in the art (see page 3 of declaration) . However, declaration of Dr. Drosschedi is not commensurate with scope of the claims because claimed method also read on producing single heavy chain antibody by somatic gene delivery or by using ES cell using BAC or YAC as vector, which is clearly not taught by the cited reference. The reference of Kuroiwa et al is limited to making a transchromosomic calves by using human artificial chromosome (HAC) vector and nuclear transfer technique. Prior to filing of instant application, Kuriowa et al (Nature Biotechnology, 18:1086-1090, 2000) taught unpredictability of using fragments of human chromosomes as vectors. Kuriowa et

al state, "Human chromosomes (hChrs) or their fragments have been used to introduce large segments of human genomic DNA into mice. However, it has been reported that the mitotic stability of hChrs in mice varies among human chromosomes. Thus, it is difficult to stably maintain any type of human chromosome in order to perform functional analyses in mice. Furthermore, it is difficult to introduce defined regions of human chromosomes into mice because the fragmentation of human chromosomes can occur randomly (page 1086, col. 1, paragraph 2)". In the instant case, specification fails to teach using any human chromosome comprising any loci that are genetically transmissible in any species of nonhuman mammal. Additionally, at the time of invention while reviewing strategies to engineer human chromosome, Saffery et al (J Gene Med. 2002 Jan-Feb;4(1):5-13) describe problems associated with the production of useful human engineered chromosome (HEC) including size and difficult to fully characterize, especially those containing highly repetitive DNA (see page 11, column 2, lines 4-15). It is noted that Saffery et al state that "the large size of HECs also makes them difficult to manipulate in terms of the introduction of genes and the transfer from cell to cell in an intact form. Present methodologies do not readily lend themselves to delivering chromosomes of this size to in vivo cell targets" (see page 12, column 1, paragraph 1). Saffery et al assert that the lack of control over their mode of formation produces the same drawbacks as HECs derived using de novo approaches, which does not permit control over gene copy number or the structural integrity of the genes incorporated into the HECs (see page 8, paragraph 1, lines 101-20). The specification does not provide any guidance how claimed method would be practiced to make and use of the invention. Furthermore, method disclosed by Kuriowa uses nuclear transfer technique, and issues pertaining to NT have been discussed in preceding section. Yanagimachi et al (Molecular and Cellular Endocrinology, 2002, 187, 241-248) state that "perhaps no single protocol for cloning that works for all mammalian species, because, the characteristics of an oocyte and

donor cells are different from species to species. A protocol that is best for a given species may not be suitable for another species. Technical details must be worked out for each species". It is emphasized that applicants have provided no guidance with regard to nuclear transfer. The specification as filed is not enabling for the claimed invention because the state of the art of producing nonhuman mammal from any donor cell into any recipient cell and transfer of HAC in a cell that develops into embryo in a female nonhuman animal was not predictable and an artisan would have required extensive experimentation to practice the claimed invention and such experimentation would have been undue since the experimentation was not routine, and the state of the art was unpredictable and the specification did not teach how to address the limitation and unpredictable nature of the invention.

The declaration by Dr. Drosschedi is persuasive to the extent one skilled in the art would be able to express any heterologous transgenic loci comprising any tissue specific regulatory sequence (see page 5). However, the declaration by Dr. Drosschedi is not commensurate with the scope of the claim. Specifically, Dr. Drosschedi concludes that the introduction of transgenes into the germ-line of non-human mammalian systems was well established were known in the art. In the instant case, as stated before, contrary to Dr. Drosschedi declaration claims are not limited to germ-line of non-human mammalian systems rather it reads on producing antibody in a nonhuman mammal by somatic gene delivery and neither specification nor prior art provide adequate guidance to one skilled in art to make and use the invention. The specification provides no specific guidance or working examples to allow an artisan to overcome art-recognized unpredictability of delivering heterologous VHH loci such as one described in the instant application other then pronuclear injection. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in art to make and use the invention as claimed without a reasonable expectation of success.

Examiner would agree with the declaration by Drs. Weiner and Grosveld to the extent the genetic background used would have no bearing on the expression or otherwise of heavy chain only antibody in the method of producing single chain heavy antibody taught by Janssens. However, as stated before claims are not limited to methods that produce single heavy chain antibody by the method taught by Janssens. Furthermore, it is not apparent from the declaration whether single chain heavy antibody obtained from wild type animal is complexed with endogenous immunoglobulin of nonhuman mammal particularly since specification does not teach characterization of any resulting single heavy chain antibody obtained by immunizing any nonhuman mammal as embraced by the breadth of the claims that has any enabled use as supported by the observations in the art record.

Withdrawn-Claim Rejections- - 35 USC § 112

Claims 2, 4, 7-8, 10-11, 33-36 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is withdrawn in view of amendments to the claims

Withdrawn-Claim Rejections- 35 USC § 102

Claim 2 rejected under 35 U.S.C. 102(b) as being anticipated by Ledbetter et al (WO 99/42077, dated 08/26/1999, IDS) is withdrawn in view of declaration by the Drs. Weiner. Examiner would agree that Ledbetter et al does not enable the production of antibody in response to antigen challenge from a heavy chain only locus in a transgenic animal and, therefore, would not anticipate the claims

Withdrawn-Double Patenting

Claims 1-4, 7-8, 10-11 and 33-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 7-8, 10-11 and 33-36 of copending Application No. 10/692,918 is withdrawn in view terminal disclaimer filed by the applicants that has been approved and recorded.

Conclusion

No claims allowed

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Lonberg et al (US Patent No. 5569825, dated 10/29/1996, art of record).

Green et al (20030093820, dated 11/30/2001, art of record)

Riechmann et al (J Immunol Methods. 1999; 231(1-2): 25-38, art of record).

Imam et al (2000) *Nucleic Acids Res* 15, E65.

Nguyen, et al (1999) Mol Immunol 36, 515–524.

Nguyen et al (2000) EMBO J 19, 921–930.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
AU 1632

/Thaian N. Ton/
Primary Examiner, Art Unit 1632